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## CONCISE COMMUNICATIONS

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### Chronic fatigue syndrome in patients with macrophagic myofasciitis

Macrophagic myofasciitis (MMF), a condition first reported in France in 1998, is defined by the presence of a stereotyped and immunologically active lesion at deltoid muscle biopsy (1,2). It was recently demonstrated that this lesion is an indicator of long-term persistence of the immunologic adjuvant aluminum hydroxide within the cytoplasm of macrophages at the site of previous intramuscular (IM) injection (2). MMF is typically detected in patients with diffuse arthralgias that have appeared subsequent to aluminum hydroxide administration in the absence of a clearly defined anatomic substratum (2). Patients also report unexplained chronic fatigue (1). These manifestations are reminiscent of the so-called chronic fatigue syndrome (CFS), a poorly understood condition manifesting as disabling fatigue, musculoskeletal pain, sleep disturbance, impaired concentration, and headaches (3). The present study was conducted to determine the proportion of MMF patients fulfilling international criteria for CFS.

Thirty unselected consecutive patients with biopsy-proven MMF identified in Créteil and Bordeaux were retrospectively included, regardless of symptoms that led to indication of muscle biopsy. As previously described (2), MMF was assessed by 1) well-circumscribed sheets of densely packed, large, nonepithelioid macrophages with a finely granular, periodic acid-Schiff-positive content, in the connective structures of deltoid muscle; 2) lymphocytic infiltrates intermingled with macrophages and forming microvascular cuffs; and 3) absence of significant muscle fiber injury (see Figure 1). In each patient, we determined, through both chart review and either direct patient questioning or telephone interview, 1) the presence of chronic fatigue of >6 months' duration, 2) the alleged severity of fatigue, and 3) the presence of CFS according to Centers for Disease Control and Prevention (CDC) criteria (1994) (4) or Oxford criteria (1991) (5). In addition, in 20 patients, we retrospectively evaluated history of immunization as well as prevalence of fever and neurologic features suggestive of central nervous system demyelinating disease; laboratory findings, including erythrocyte sedimentation rate, creatine kinase levels, and  $^{67}\text{Ga}$  scintigraphy; and responsiveness to steroids.

The male:female ratio was 1:2. The mean age of patients was 52 years (range 12-78 years). Chronic fatigue was found in 28 of 30 patients (93%) and was considered disabling in 26 of 30 patients (87%). Sixteen patients (53%) fulfilled CFS criteria from either the CDC (14 of 30 patients, 47%) or Oxford (12 of 30 patients, 40%), 11 of 30 patients (37%) fulfilled both CDC and Oxford criteria. Other symptoms, laboratory findings, and steroid responsiveness are detailed in Table 1.  $^{67}\text{Ga}$  scintigraphy was performed in 5 patients and showed increased levels of  $^{67}\text{Ga}$  uptake in muscle and pararticular areas, mainly in lower limbs. A history of vaccination was available for 19 of 20 patients. All 19 patients had received

IM administration of aluminum-containing vaccine prior to the onset of CFS symptoms, and the delay from the last vaccination to the first manifestations ranged from 1 month to 72 months (median 12 months).

We have previously determined that myalgias are a major symptom in patients with MMF. The prevalence of myalgias was much higher in such patients than in other patients who had undergone deltoid muscle biopsies at the same time in the same centers (85% versus 45%;  $P < 0.0001$  by Fisher's exact test) (2). We show now that chronic disabling fatigue is a symptom as frequent as diffuse myalgias in patients with MMF (87%), a finding also noted in the French Institut de Veille Sanitaire exploratory investigation report (6). More than half of the patients also reported other manifestations of CFS. Therefore, MMF should be alternatively considered as a cause of CFS or as an additional exclusion criterion, along with rheumatoid arthritis, lupus, and other diseases, for the diagnosis of idiopathic CFS (4). Consequently, we suggest that patients with CFS should be carefully checked for a history of IM administration of aluminum hydroxide, and, if there is consistent chronology, a muscle biopsy to search for MMF at the site of injection should be considered, even many years after onset of symptoms.

Pathophysiology of CFS is still fiercely debated by psychologists, neuroendocrinologists, and immunologists. Chronic immune stimulation that fails to switch off has been previously reported as a possible cause of CFS (7-9), and such a situation may very well result from persistence of the immunologic adjuvant aluminum hydroxide within antigen-presenting cells (2,10). Therefore, MMF may well represent a paradigm for CFS of immunologic origin. We believe that clarification of MMF pathophysiology would significantly contribute to the understanding of the whole spectrum of chronic fatigue and its syndromes.

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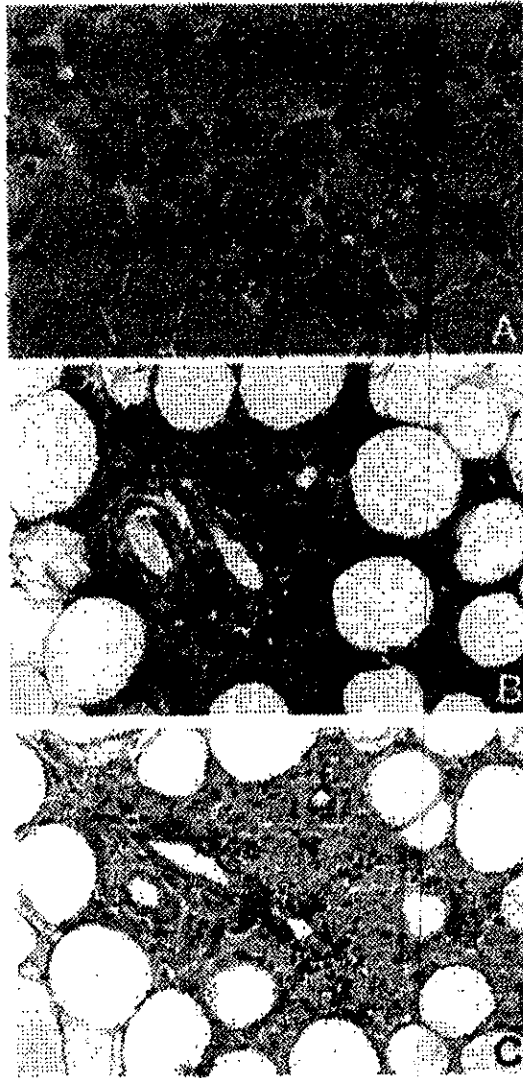


Figure 1. Deltoid muscle biopsy samples from patients with macrophagic myofasciitis (MMF). A, Tightly packed, large, basophilic macrophages intermingled with lymphocytes in perifascicular endomysium (frozen section, hematoxylin and eosin stained; original magnification  $\times 400$ ). B, MMF lesion in perifascicular adipose tissue showing immunolocalization of the macrophage marker CD68 (paraffin section, immunoperoxidase procedure; original magnification  $\times 400$ ). C, Adjacent section of the same biopsy sample showing immunolocalization of the T cell marker CD3 (paraffin section, immunoperoxidase procedure; original magnification  $\times 400$ ).

Table 1. Clinical and laboratory findings in patients with macrophagic myofasciitis\*

Chronic fatigue†	28/30 (93)
Severe and disabling	26/30 (87)
Of new onset	25/30 (83)
Leading to substantial reduction in previous levels of activity	24/30 (80)
Present for >50% of the time	19/30 (63)
Not a result of ongoing exertion	18/30 (60)
Affecting both physical and mental functioning	16/30 (53)
Not substantially alleviated by rest	13/30 (43)
Other symptoms†	
Muscle pain	26/30 (87)
Joint pain	17/30 (57)
Sleep disturbance	16/30 (53)
Mood disturbance	16/30 (53)
Subjective memory impairment	15/30 (50)
Headache	14/30 (47)
Unrefreshing sleep	14/30 (47)
CFS criteria fulfilled	14/30 (53)
CDC (1994) (see ref. 4)	14/30 (47)
Oxford (1991) (see ref. 5)	12/30 (40)
Neurologic features suggestive of CNS demyelinating disease	2/20 (10)
Fever	2/20 (10)
Abnormal laboratory findings	
ESR >40 mm/hour	2/14 (14)
CK level >200 IU/liter	4/14 (29)
$^{67}\text{Ga}$ scintigraphy	5/5 (100)
Responsive to steroids‡	10/10 (100)

\* Values are the number (%) of patients. CFS = chronic fatigue syndrome; CDC = Centers for Disease Control and Prevention; CNS = central nervous system; ESR = erythrocyte sedimentation rate; CK = creatine kinase.

† Part of diagnostic criteria for CFS.

‡ Improvement of both fatigue and myalgia. One patient received intravenous methylprednisolone without significant effect.

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